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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/647,780	12/26/2000	Tanja Ouimet	P06910US00/BAS	3825
881	7590	06/16/2004	EXAMINER	
STITES & HARBISON PLLC 1199 NORTH FAIRFAX STREET SUITE 900 ALEXANDRIA, VA 22314			WALICKA, MALGORZATA A	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.

09/647,780

Applicant(s)

OUMET ET AL.

Examiner

Malgorzata A. Walicka

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--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 24 May 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☒ The proposed amendment(s) will not be entered because:
- (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ they raise the issue of new matter (see Note below);
- (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: raise 35 USC 112 2nd paragraph issues as to whether the "ECE/NEP/Kell family" is definite.

3. ☒ Applicant's reply has overcome the following rejection(s): none.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: see the attached.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☒ will not be entered or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: 1-6, 11 and 13.

Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.
10. ☐ Other: _____

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The amendment filed on May 24, 2004 under 37 CFR 1.116 in reply to the final rejection has been considered but is not deemed to place the application in condition for allowance and will not be entered because:

it raises issues under 35 USC section 112 second paragraph, and does not overcome rejections under 35 USC, first paragraph for lack of written description and scope of enablement, and rejection under USC section 102(b) made in the Final Office Action of February 24, 2004.

1. Rejections

1.1. 35 USC section 112, first paragraph

3.3.1. Lack of written description

Claim 1, 6, 11 and 13, are rejected under 35 U.S.C. 112, first paragraph, for reasons stated in the previous Office Action. Applicants attention is turned to the fact that SEQ ID NO: 3 is not encoding an active center of the enzyme and is only a partial sequence. Similarly Peptide of SEQ ID NO: 4 is not an active peptide, but only a peptide of not described structure that is comprised. The peptide comprising SEQ ID NO: 4 is claimed as the invention. Thus, claims are directed to a large and variable genus of polypeptides that were not in possession of Applicants at the time the instant application was filled.

In their response Applicants argue,

"one of ordinary skill in the art would readily appreciate and easily discern the structure of the claimed polypeptide recited as having an amino acid sequence encoded by nucleic acid sequence SEQ ID NO: 3 where the polypeptide is a membrane-bound metalloprotease referred to as NEP2 and belonging to the endotelin converting enzyme/neprilysin/Kell family. Specifically, the specification allows one skilled in the art to determine the sequence of the NEP2 polypeptide and thus the structure of the claimed polypeptide", Remarks, page 2 the third paragraph.

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Firstly, whether specification allows one skilled in the art to determine the sequence of the NEP2 polypeptide and thus the structure of the claimed polypeptide is a question of enablement and not written description. However, if someone sequences a protein that starts with SEQ ID NO: 4, that does not mean that he/she is able to identify all claimed genus of sequences comprising said sequence that will have metalloprotease activity. The same argument goes for enablement of nucleotide sequences comprising SEQ ID NO: 3; see page 4 line 3 of the Remarks.

Applicants also state, "Furthermore, the present specification does describe how to encode a polypeptide with the disclosed functionality using SEQ ID NO: 3" (Remarks, page 4, the last paragraph). Applicants' argument is fully considered but is not found persuasive for the reasons given above. If SEQ ID NO: 4 were the active part of the enzyme, applicants' argument would have been persuasive. However, SEQ ID NO: 4 is not disclosed as having metalloprotease activity.

1.2. Scope of enablement

Claims 1, 6, 11 and 13, remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide identified by SEQ ID NO: 4, does not reasonably provide enablement for all peptides that comprise a polypeptide encoded by SEQ ID NO: 3. Applicants did not provide any guidance as to the structure of polypeptide comprising amino acid sequence encoded by SEQ ID NO: 3, i.e., a full size enzyme and its variants. For the same reasons the specification is missing any instructions as to how to construct a polypeptide having a neprilysin activity wherein amino acid sequence encoded by SEQ ID NO: 3 constitute the only known fragment of said polypeptide. Without further guidance on the part of Applicants as to the structure of the claimed polypeptide experimentation left to those skilled in the art is improperly extensive and undue.

1.3. 35 USC, 102

Claim 6 remains rejected under 35 U.S.C. 102(b) for the reasons stated in the previous Office Actions mailed Feb. 24, 2004, July 9, 2003 and December 3, 2002.

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Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by Shipp et al. (Molecular cloning of the common acute lymphoblastic leukemia antigen (CALLA) identifies type II integral membrane protein, Proc. Natl. Acad. Sci. USA, 1988, 85, 4819-4823, and Ritz et al. (A monoclonal antibody to human acute lymphoblastic leukaemia antigen, Nature 1980, 283, 583-585.

The amended claim 6 is directed to mono-or polyclonal isolated antibodies or their fragments, chimeric isolated antibodies or immunoconjugates, characterized in that they are obtained using a polypeptide and are capable of recognizing specifically a polypeptide comprising the amino acid sequence encoded by SEQ ID NO: 3.

Shipp et al., page 4821, Fig. 2, teach a protein called CALLA antigen containing in positions 583-696 the amino acid sequence identical in 66.7% to amino acid residues 1-114 of SEQ ID NO: 4 (SEQ ID NO: 4 comprises the polypeptide encoded by SEQ ID NO: 3 in positions 1-109). Ritz et al. teach production of monoclonal antibody against CALLA. Ritz et al teach the invention of claim 6, because the antibody specific to the sequence that is 66.7% identical to SEQ ID NO: 4 will combine to SEQ ID NO: 4 or any polypeptide containing amino acid sequence encoded by SEQ ID NO: 3. Those skilled in the art realize that an antibody "cross-reacts", i.e. binds to more than one protein sequence, which means that specifically recognize more than one protein. For example, Bost et al. (Antibodies against a Peptide Sequence within the HIV Envelope Protein Crossreact with Human Interleukin-2, Immunological Investigations, (1988, 17, pages 577-586; see the attached in the Final Rejection) have shown that one kind of antibodies reacts with two different proteins, because of the presence in their sequences of homologous fragments, consisting of **4-6 identical amino acid residues**. Such short sequences of amino acids consist what is called antibody's epitope. As evidenced in the alignment of CALLA and SEQ ID NO: 4 of the instant application sent to the Applicants previously, CALLA and SEQ ID NO: 4, or for that matter a sequence encoded by SEQ ID NO: 3, have more than one fragment consisting of more than 10 identical amino acids.

In their Remarks, page 5, line 11, Applicants write, "Shipp and Riz [!] clearly teach antibodies which react with additional polypeptides other than polypeptide according to claim 1. Thus the antibodies of Ship and Ritz are not 'capable of recognizing specifically a peptide of claim 1.' Since the antibodies

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disclosed by in Shipp et al. and Ritz et al. fail to be specific, i.e. only bind, and recognize the polypeptide of claim 1, the disclosed antibodies in Shipp et al., Ritz et al. do not anticipate the antibodies of claim 6."

This argument of Applicants has been fully considered, but is found not persuasive. Although the antibodies of the prior art has not been obtained using a polypeptide comprising a sequence encoded by SEQ ID NO: 3 i.e. they definitely will cross react (recognize and bind) with polypeptides comprising a sequence encoded by SEQ ID NO: 3.

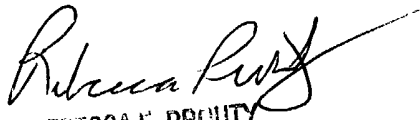
Since the Office does not have a laboratory to test the reference by Ritz et al., it is Applicant's burden to show that the reference antibodies do not bind to a polypeptide comprising the amino acid sequence encoded by SEQ ID NO: 3 as recited in the claim. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); *In re Fitzgerald et al.*, 205 USPQ 594 (CCPA 1980).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (571) 272-0944. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (571) 272-0928. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.
Patent Examiner
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